National Institute of Neurological Disorders and Stroke

Machado-Joseph Disease Fact Sheet

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What is Machado-Joseph Disease?

Machado-Joseph disease (MJD)-also called spinocerebellar ataxia type 3-is a rare hereditary ataxia. (Ataxia is a general term meaning lack of muscle control.) The disease is characterized by clumsiness and weakness in the arms and legs, spasticity, a staggering lurching gait easily mistaken for drunkenness, difficulty with speech and swallowing, involuntary eye movements, double vision, and frequent urination. Some patients have dystonia (sustained muscle contractions that cause twisting of the body and limbs, repetitive movements, abnormal postures, and/or rigidity) or symptoms similar to those of Parkinson's disease. Others have twitching of the face or tongue, or peculiar bulging eyes.

The severity of the disease is related to the age of onset, with earlier onset associated with a more severe form of the disease. Symptoms can begin any time between early adolescence and about 70 years of age. MJD is also a progressive disease, meaning that symptoms get worse with time. Life expectancy ranges from the mid-thirties for those with severe forms of MJD to a normal life expectancy for those with mild forms. For those who die early from the disease, the cause of death is often aspiration pneumonia.

The name, Machado-Joseph, comes from two families of Portuguese/Azorean descent who were among the first families described with the unique symptoms of the disease in the 1970s. The prevalence of the disease is still highest among people of Portuguese/Azorean descent. For immigrants of Portuguese ancestry in New England, the prevalence is around one in 4,000. The highest prevalence in the world, about one in 140, occurs on the small Azorean island of Flores. Recently, researchers have identified MJD in several family groups not of obvious Portuguese descent, including an African-American family from North Carolina, an Italian-American family, and several Japanese families. On a worldwide basis, MJD is the most prevalent autosomal dominant inherited form of ataxia, based on DNA studies.

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What are the different types of Machado-Joseph Disease?

The types of MJD are distinguished by the age of onset and range of symptoms. Type I is characterized by onset between 10 and 30 years of age, fast progression, and severe dystonia and rigidity. Type II MJD generally begins between the ages of 20 and 50 years, has an intermediate progression, and causes symptoms that include spasticity (continuous, uncontrollable muscle contractions), spastic gait, and exaggerated reflex responses. Type III MJD patients have an onset between 40 and 70 years of age, a relatively slow progression, and some muscle twitching, muscle atrophy, and unpleasant sensations such as numbness, tingling, cramps, and pain in the hands, feet, and limbs. Almost all MJD patients experience vision problems, including double vision (diplopia) or blurred vision, loss of ability to distinguish color and/or contrast, and inability to control eye movements. Some MJD patients also experience Parkinson's-like symptoms, such as slowness of movement, rigidity or stiffness of the limbs and trunk, tremor or trembling in the hands, and impaired balance and coordination.

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What causes Machado-Joseph Disease?

MJD is classified as a disorder of movement, specifically a spinocerebellar ataxia. In these disorders, degeneration of cells in an area of the brain called the hindbrain leads to deficits in movement. The hindbrain includes the cerebellum (a bundle of tissue about the size of an apricot located at the back of the head), the brainstem, and the upper part of the spinal cord. MJD is an inherited, autosomal dominant disease, meaning that if a child inherits one copy of the defective gene from either parent, the child will develop symptoms of the disease. People with a defective gene have a 50 percent chance of passing the mutation on to their children.

MJD belongs to a class of genetic disorders called triplet repeat diseases. The genetic mutation in triplet repeat diseases involves the extensive abnormal repetition of three letters of the DNA genetic code. In the case of MJD the code "CAG" is repeated within a gene located on chromosome 14q. The MJD gene produces a mutated protein called ataxin-3. This protein accumulates in affected cells and forms intranuclear inclusion bodies, which are insoluble spheres located in the nucleus of the cell. These spheres interfere with the normal operation of the nucleus and cause the cell to degenerate and die.

One trait of MJD and other triplet repeat diseases is a phenomenon called anticipation, in which the children of affected parents tend to develop symptoms of the disease much earlier in life, have a faster progression of the disease, and experience more severe symptoms. This is due to the tendency of the triplet repeat mutation to expand with the passing of genetic material to offspring. A longer expansion is associated with an earlier age of onset and a more severe form of the disease. It is impossible to predict precisely the course of the disease for an individual based solely on the repeat length.

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How is Machado-Joseph Disease diagnosed?

Physicians diagnose MJD by recognizing the symptoms of the disease and by taking a family history. They ask detailed questions about family members who show, or showed, symptoms of the disease, the kinds of symptoms these relatives had, the ages of disease onset, and the progression and severity of symptoms. A definitive diagnosis of MJD can only be made with a genetic test. Unfortunately, many legal and ethical considerations, such as loss of health insurance and employment discrimination, may discourage some individuals with symptoms from getting tested. For the same reasons, many physicians recommend against genetic testing for those individuals who have a family history of the disease but do not show symptoms. For more information on genetic testing and counseling, please consult the organizations listed in the section titled "Where can I get more information?"

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How is Machado-Joseph Disease treated?

ATTACHMENT "A"

MJD is incurable, but some symptoms of the disease can be treated. For those patients who show parkinsonian features, levodopa therapy can help for many years. Treatment with antispasmodic drugs, such as baclofen, can help reduce spasticity. Botulinum toxin can also treat severe spasticity as well as some symptoms of dystonia. However, botulinum toxin should be used as a last resort due to the possibility of side effects, such as swallowing problems (dysphagia). Speech problems (dysarthria) and dysphagia can be treated with medication and speech therapy. Wearing prism glasses can reduce blurred or double vision, but eye surgery has only short-term benefits due to the progressive degeneration of eye muscles. Physiotherapy can help patients cope with disability associated with gait problems, and physical aids, such as walkers and wheelchairs, can assist the patient with everyday activities. Other problems, such as sleep disturbances, cramps, and urinary dysfunction, can be treated with medications and medical care.

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What research is being done?

The National Institute of Neurological Disorders and Stroke (NINDS) supports research on MJD and other neurodegenerative diseases in an effort to learn how to better treat, prevent, and even cure these diseases. Ongoing research includes efforts to better understand the genetic, molecular, and cellular mechanisms that underlie triplet repeat diseases. Other research areas include the development of novel therapies to treat the symptoms of MJD, efforts to identify diagnostic markers and to improve current diagnostic procedures for the disease, and population studies to identify affected families.

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Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
(800) 352-9424
http://www.ninds.nih.gov

Information also is available from the following organizations:

National Ataxia Foundation (NAF)
2600 Fernbrook Lane North
Suite 119
Minneapolis, MN 55447-4752
naf@ataxia.org
http://www.ataxia.org
Tel: 763-553-0020
Fax: 763-553-0167

National Organization for Rare Disorders (NORD)
P.O. Box 1968
(55 Kenosia Avenue)
Danbury, CT 06813-1968
orphan@rarediseases.org
http://www.rarediseases.org
Tel: 203-744-0100 Voice Mail 800-999-NORD (6673)
Fax: 203-798-2291

Dystonia Medical Research Foundation
1 East Wacker Drive
Suite 2430
Chicago, IL 60601-1905
dystonia@dystonia-foundation.org
http://www.dystonia-foundation.org
Tel: 312-755-0198
Fax: 312-803-0138

National Aphasia Association
350 Seventh Ave.
Suite 902
New York, NY 10001
naa@aphasia.org
http://www.aphasia.org
Tel: 212-267-2814 800-922-4NAA (4622)
Fax: 212-267-2812

American Speech-Language-Hearing Association (ASHA)
10801 Rockville Pike
Rockville, MD 20852-3279
actioncenter@asha.org
http://www.asha.org
Tel: 800-638-8255
Fax: 301-571-0457

Family Caregiver Alliance/ National Center on Caregiving
180 Montgomery Street
Suite 1100
San Francisco, CA 94104
info@caregiver.org
http://www.caregiver.org
Tel: 415-434-3388 800-445-8106
Fax: 415-434-3508

National Family Caregivers Association
10400 Connecticut Avenue
Suite 500
Kensington, MD 20895-3944
info@thefamilycaregiver.org
http://www.thefamilycaregiver.org
Tel: 301-942-6430 800-896-3650
Fax: 301-942-2302

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